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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/655,905	09/05/2003	Marvin R. Garovoy	P1747R2D1	7684

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EXAMINER	
HADDAD, MAHER M	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 09/10/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/655,905	GAROVOY ET AL.	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 August 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *9/5/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-15 are pending.

2. Applicant's election without traverse of Group I, claims 1-14 drawn to a method for reducing the occurrence of fever, headache, nausea and/or vomiting associated with administration of a therapeutic compound to a mammal in need comprising administering to the mammal a therapeutic compound which binds to a cell surface receptor on a target mammalian cell wherein the therapeutic compound an antibody against CD11a and psoriasis as the species, filed on 8/9/04, is acknowledged.

Upon reconsideration the Examiner extended the search to include asthma, transplant rejection, rheumatoid arthritis, systemic lupus erythmatosus and multiple sclerosis.

3. Claims 1-15 are under examination as they read on a method for reducing the occurrence of fever, headache, nausea and/or vomiting associated with administration of a therapeutic compound to a mammal in need comprising administering to the mammal a therapeutic compound which binds to a cell surface receptor on a target mammalian cell wherein the therapeutic compound an antibody against CD11a and psoriasis, asthma, transplant rejection, rheumatoid arthritis, systemic lupus erythmatosus and multiple sclerosis as the species.

4. The specification on page one should be amended to reflect the status of Application No. 09/936,603.

5. Claims 1-15 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

It is apparent that the hybridoma that produce the hu1124 antibody recited in claim 7 is required to practice the claimed invention. As a required element, it must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. If it is not so obtainable or available, the enablement requirements of 35 USC 112, a deposit of the hybridoma, which produces this antibody, may satisfy first paragraph. See 37 CFR 1.801-1.809.

If the deposit has been made under the terms of the Budapest Treaty, an affidavit or declaration by applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the hybridoma has been deposited under the Budapest Treaty and that the hybridoma will be irrevocably and without restriction or condition released to the public upon the issuance of a patent would satisfy the deposit requirement made herein. See 37 CFR 1.808. Further, the record must be clear that the deposit will be maintained in a public depository for a period of 30 years after the date of deposit or 5 years after the last request for a sample *or for the enforceable life of*

the patent whichever is longer. See 37 CFR 1.806. If the deposit has not been made under the Budapest treaty, then an affidavit or declaration by applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature much be made, stating that the deposit has been made at an acceptable depository and that the criteria set forth in 37 CFR 1.801-1.809, have been met.

If the deposit was made after the effective filing date of the application for a patent in the United States, a verified statement is required from a person in a position to corroborate that the hybridoma described in the specification as filed are the same as that deposited in the depository. Corroboration may take the form of a showing of a chain of custody from applicant to the depository coupled with corroboration that the deposit is identical to the biological material described in the specification and in the applicant's possession at the time the application was filed.

Further, amendment of the specification to disclose the date of deposit and the complete name and address of the depository (ATCC.10801 University Boulevard, Manassas, VA 20110-2209) is required as set forth in 37 C.F.R. 1.809(d).

Further, the specification does not reasonably provide **enablement** provide enablement for a method for treating the occurrence of fever, headache, nausea and or vomiting associated with administration of a "therapeutic compound" to a mammal comprising administering to a mammal a first "conditioning dose" of a non-target cell-depleting compound which binds to a "cell surface receptor" on a target mammalian cell; and followed by a higher dose in claim 1; wherein the "compound" comprises any polypeptide which binds to any "extracellular domain of the receptor molecule" in claim 2; wherein the "polypeptide" is any antibody or a receptor binding fragment thereof in claim 3. The specification does not enable any person skilled in the art to which it pertains, wherein the antibody is administered for the treatment of any transplant rejection in claim 14, rheumatoid arthritis, systemic lupus erythmatosus or multiple sclerosis in claim 15. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with this claim.

The specification disclosure does not enable one skilled in the art to practice the invention without an undue amount of experimentation.

It is not seen that a patient receiving a therapeutic compound e.g., OKT3 antibody treatment followed by anti-CD11a antibody to reduce the side effect occurrence of fever, headache, nausea and/or vomiting because OKT3 rapidly reduces the number of circulating T cells. Further, a well know drugs such as Aspirin, Tylenol, Panadol, ibuprophine or the like would the choice of such occurrence of fever, headache, nausea and or vomiting. Further, the specification lack examples showing a reduction of the occurrence of fever, headache, nausea and or vomiting associated with any other therapeutic compound such as OKT3 antibody. The specification discloses examples of treatment of psoriasis, asthma and kidney transplant rejection with hu1124 (anti-CD11a) which found to reduce the side effects associated with the treatment of those disease.

Besides anti-CD11a antibody, the specification fails to provide any guidance as to how to make and how to use any "therapeutic compound", any "extracellular domain the receptor", any "antibody" or any "receptor binding fragment thereof". The specification discloses the administration of the anti-CD11a antibodies in a dosing regiment which introduces an initial low "conditioning dose" followed by a higher dose designed for the therapeutic treatment of psoriasis, asthma and renal transplant. However, the specification disclosure is limited to working examples using only anti-CD11a antibody and is silent with respect to the features required of the genus of both the "therapeutic compound" and compounds which are non-target cell depleting compound which binds cell-surface receptor such that they can used in a manner commensurate with the full scope of the claims. Further, the examples are silent regarding compounds that bind to intact any cell surface receptor.

The claims require that the method for reducing occurrence of fever, headache, nausea and/or vomiting to be associated with administration of a "therapeutic compound" to a mammal in need. However, the only therapeutic compound is exemplified is the non-depleting anti-CD11a antibody. The specification on page 1, lines 26-35 discloses that one compound associated with adverse side effects (e.g. fever, chills, nausea, vomiting and tightness of the chest) is the murine monoclonal antibody OKT3. OKT3 binds to CD3 protein complex that is associated with the T cell receptor (TCR) found on the surface of all T lymphocytes. Administration of OKT3 to humans rapidly reduces the number of circulating T cells (e.g. OKT3 is a cell depleting compound) and reduces the mount of cell surface TCR found on those T cells that remain. While the treatment with OKT3 eliminates the target T cells, it is not seen how the non-T lymphocyte-depleting anti-CD11a antibody would reduce the side effect (e.g. fever, headache, nausea and/or vomiting) in the already depleted T cells patients. Furthermore, while the specification discloses that these side effects are believed to be caused by cytokine release from T cells due to OKT3-induced activation and complement activation (see page 1, lines 35-37), it is not seen how would anti-CD11a antibodies inhibit the release of these cytokine from activated T cells by the OKT3. Further, the specification on page 2, lines 9-21, discloses that a humanized anti-CD-4 monoclonal antibody induced fever, chills, hypotension and chest tightness when given intravenously to psoriasis and RH patients. The specification further discloses that this treatment down-modulated expression of CD4 and caused a reduction in the number of circulating CD4-positive T cells and but was not completely depleting. Similarly, the anti-CD64 antibodies. However, it is not seen how the non-T cell depleting antibody to CD11a would reduce the release of cytokines that causes these side effect (whether the cytokine released from the T cells or plasma). Therefore, besides the non-T cell depleting anti-CD11a therapeutic compound, the specification fails to provide other therapeutic compounds that associated with these side effects which can be treated with the non-lymphocyte depleting CD11a antibody.

The current state of the art in antibody therapeutics and the predictability of treatment efficacy is complicated by the potential for antibody interactions with irrelevant or completing epitopes, Fc region engagement, reduced half life of antibody fragments, and immune response to the therapeutic antibodies (see Ward et al, pages 167-171, "consideration related to use of blocking

antibodies" PTO Form 1449, Ref # 75). Furthermore, Isaacs et al. (PTO Form 1449, Ref # 53) notes that the lymphocytotoxicity, i.e. target-cell depletion capability, of different therapeutic antibodies is not predictable by standard in vitro testing methods and may depend on their epitope specificity, affinity or other undefined features (see page 164, "discussion" in particular).

Claims 1-5 require a "non-target-cell compound" to bind to any surface receptor or lymphocyte surface receptor such as LFA-1 which includes its subunits CD11a and CD18. However, the present specification fails to provide sufficient disclosure of compounds that maintain the functional properties to bind the lymphocyte surface receptor, wherein the compound comprises a polypeptide which binds to an extracellular domain of the receptor. Beside an antibody to CD11a subunit of LFA-1, the specification does not provide sufficient guidance as to which of the compounds may be administered to a mammal while their functional activity is retained.

Therefore, one skilled in the art at the time of the invention would not be able to predict which compounds such as antibodies are non-target cell depleting and which will elicit a first-dose reaction. Consequently the skilled artisan would not know how to use the instant invention as broadly claimed. While experimental testing techniques using cell surface receptor binding compounds are available, it is not routine in the art to use such methods when the expectation of success is unpredictable based on the instant disclosure. Thus, it would require an undue amount of experimentation of one skilled in the art to practice the invention as broadly claimed.

Also, at issue is whether or not the claimed method would function for treating "rheumatoid arthritis, multiple sclerosis, and rejection by a[ny] transplanted graft". The nature of the invention is such that it would require the administration of an anti-CD11a antibody in a dosing regime which introduces an initial low "conditioning dose" followed by a higher dose designed for the reducing the side effect of therapeutic treatment of psoriasis, asthma and renal transplant. The specification discloses administering a low dose first treatment of anti-CD11a antibody followed by a higher dose of anti CD11a antibody to a subject to act as a treatment for psoriasis, asthma and renal transplantation. The exemplification is drawn to decrease in the severity of the psoriasis, show efficacy in treating asthma and reduce graft rejection with low incidence of headache and fever.

In re Fisher, 166 USPQ 18 indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. Since no animal model were used to treat rheumatoid arthritis, multiple sclerosis, and rejection by any transplanted graft (except for renal transplant). Even when such animal model studies used they do not correlated well with in vivo clinical trial results in patients. Since the method of treating indices of administering to the animal an anti-CD11a can be species- and model-dependent, it is not clear that reliance on treating other diseases such as psoriasis using the anti-CD11a antibody accurately reflects the relative human efficacy of reducing fever, headache, nausea and/or vomiting in other disorders such as rheumatoid arthritis, multiple sclerosis, and rejection by a transplanted graft. Therefore, it is not clear that the skilled artisan could predict the efficacy of the antibody on the reducing the side effect associated with administration of a therapeutic compound in the treatment of rheumatoid arthritis, multiple sclerosis, and rejection by a transplanted graft.

Reasonable correlation must exist between the scope of the claims and scope of the enablement set forth. In view on the quantity of experimentation necessary the limited working examples, the nature of the invention, the state of the prior art, the unpredictability of the art and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

6. Claims 1-15 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant is in possession of for a method for a method for treating psoriasis, asthma, rejection of a transplanted renal graft and rejection by a transplanted renal graft, wherein the occurrence of fever, headache, nausea and/or vomiting is reducedcomprising administering to a mammal a first "conditioning dose" of anti-CD11a antibody or a receptor binding fragment thereof binds CD11a followed by a higher dose.

Applicant is not in possession of a method for treating the occurrence of fever, headache, nausea and or vomiting associated with administration of a "therapeutic compound" to a mammal comprising administering to a mammal a first "conditioning dose" of a non-target cell-depleting compound which binds to a "cell surface receptor" on a target mammalian cell; and followed by a higher dose in claim 1; wherein the "compound" comprises any polypeptide which binds to any "extracellular domain of the receptor molecule" in claim 2; wherein the "polypeptide" is any antibody or a receptor binding fragment thereof in claim 3. The specification does not enable any person skilled in the art to which it pertains, wherein the antibody is administered for the treatment of any transplant rejection in claim 14, rheumatoid arthritis, systemic lupus erythmatosus or multiple sclerosis in claim 15.

Applicant has disclosed only anti-CD11a antibodies; therefore, the skilled artisan cannot envision all the contemplated polypeptide compound possibilities recited in the instant claims. Consequently, conception cannot be achieved until a representative description of the structural and functional properties of the claimed invention has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC1993). The Guidelines for the Examination of Patent Application Under the 35 U.S.C.112, ¶ 1"Written Description" Requirement make clear that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 20001, see especially page 1106 3rd column).

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

7. A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

8. Claims 1-5, 10 and 12-13 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1-5 and 8-10 of copending Application No. 10/600,633. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

9. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

10. Claims 6-9, 11 and 14-15 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 6-7 and 11-22 of copending Application No. 10/600,633 in view of Owens *et al* (1994).

The teachings of `633 Application have been discussed, supra. The `663 Application further teaches that the administration of a non-target cell-depleting anti-CD11a, wherein the target mammalian cell is a lymphocyte (see claims 1 and 4 in particular). Further the `633 publication teaches the disorder is psoriasis, asthma, rheumatoid arthritis, multiple sclerosis, rejection of a transplanted graft or rejection by a transplanted graft (see claim 16) and that the fourth dose is higher or equal to the third second dose (see claim 19)

The claimed invention differs from the reference teaching only by the recitation of a humanized antibody in claim 9.

Owens *et al* teach the modification of murine antibodies such as a humanized antibody antibodies using monoclonal. Owens *et al* further teach humanized antibodies use in therapy of human diseases or disorders, since the human or humanized antibodies are much less likely to induce an immune response (see the entire document).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to produce the hu1124 antibody taught by `633 Application as humanized antibody taught by the Owens *et al.*

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because the humanized antibodies are much less likely to induce an immune response as taught by Owens *et al.*

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expection of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

This is a provisional obviousness-type double patenting rejection.

11. Claims 1-14 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-8 of U.S. Patent No. 6,582,698. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of '698 patent would anticipate the claims of the instant application; therefore Applicant is literally claiming again what has already been patented. The preamble of the conflicting claims are different however, the same product is used in the method with same method steps and patient populations, therefore the practice of the invention of '698 patent would necessarily result in the practice for the instant invention and vice versa. Therefore, the reduction of the side effects in the treatment methods are inherent to the practice of the invention of `698 patent and therefore, anticipated. Further, there are no manipulative differences between the instant claims and claims 1-8 of the `698 patent.

12. Claims 1-14 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-9 of U.S. Patent No. 6,652,855. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of '855 patent would anticipate the claims of the instant application; therefore Applicant is literally claiming again what has already been patented. The preamble of the conflicting claims are different however, the same product is used in the method with same method steps and patient populations, therefore the practice of the invention of '855 patent would necessarily result in the practice for the instant invention and vice versa. Therefore, the reduction of the side effects in the treatment methods are inherent to the practice of the invention of `855 patent and therefore, anticipated. Further, there are no manipulative differences between the instant claims and claims 1-9 of the `855 patent.

13. No claim is allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad whose telephone number is (571) 272-0845. The examiner can normally be reached Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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